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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,325	02/27/2002	Jeffrey I. Weitz	GDV-001.01	6259

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EXAMINER	
MAIER, LEIGH C	
ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 01/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,325	WEITZ ET AL.	
	Examiner	Art Unit	
	Leigh C. Maier	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/30/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 14, 2004 has been entered.

Claims 35 and 62 have been amended. Although the claims 70-80 are labeled as "new," they were in fact previously presented. Claims 35-80 are pending. Any rejection or objection not specifically repeated has been withdrawn.

The declaration under 37 CFR 1.132 has been fully considered but is moot in view of the new grounds of rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 35-39, 41-56, and 70-78 are rejected under 35 U.S.C. 102(b) as being anticipated by BRAY et al (Biochem. J., 1989) with WEITZ et al (J. Lab. Clin. Med., 1993) and HOGG et al (JBC, 1990) to support inherency.

BRAY discloses a 24-monosaccharide heparin fragment with MW of about 7200. The fragment is reported to be essentially heterogeneous, making it, by definition, a narrow polydispersity fraction. The reference also discloses a high affinity fraction having reduced polydispersity and MW of about 7800. The products are isolated by affinity chromatography on antithrombin-Sepharose, making the products necessarily enriched in the antithrombin-binding pentasaccharide. See 1st paragraph under the heading "Materials and Methods" at page 226. It is noted that in the art, given the heterogeneous nature of heparin and monosaccharide comprising it, the discussion of numeric values used for molecular weights of heparin fragments are not exceedingly consistent and precise. For example, in this reference, a 24-monosaccharide heparin fragment is said to have a MW of about 7200. On the other hand, WEITZ refers to a *23*-monosaccharide heparin fragment with MW of about *7500*. See page 365, 2nd full paragraph. Therefore, it would appear that these fragments disclosed by BRAY would be included in the range comprising "about 8000 Daltons to about 10,000 [or 12,000] Daltons" or "greater than or equal to about 7,800." (See claims 38, 39, 50-52, 70 and related dependents.) This passage in WEITZ also notes that this 23-monosaccharide heparin fragment is the minimum length necessary to bind HC II to thrombin. Furthermore, HOGG teaches that heparin species require a molecular weight of greater than about 11,200 Daltons to effectively bind thrombin to fibrin. See page 244, top of right-hand column and page 245, 3rd full paragraph. Therefore, the *inability* to bridge thrombin to fibrin would apparently be an inherent property of heparin fragments of the size disclosed by BRAY.

The reference is silent regarding values for anti-factor Xa activity, anti-factor IIa activity, or the ratio of these activities. However, the products appear to be physically consistent with the

limitations of the present claims and therefore must comprise the same physiological activity of the recited products. Since the Office does not have the facilities for preparing the claimed materials and comparing them with prior art inventions, the burden is on Applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 35-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over BRAY et al (Biochem. J., 1989) in view of WEITZ et al (J. Lab. Clin. Med., 1993) and HOGG et al (JBC, 1990).

The claims are drawn to a medium molecular weight heparins (MMWHs) having molecular weight range of about 6,000 to about 12,000 Daltons and narrower MW ranges comprised within this broad range, wherein at least 15% of said oligosaccharides have at least one pentasaccharide sequence that interacts with antithrombin. The narrowest ranges all comprise MW of about 8000. Although not stated in the claims, these MWs are interpreted as weight averages, consistent with the declaration, filed October 14, 2004. Dependents are drawn to various physical and physiological properties of the products. Also claimed are methods of treating or preventing thrombotic conditions.

BRAY teaches as set forth above. The reference further discusses generally the use of heparin products for the inhibition of thrombin and the treatment of thrombosis but does not exemplify such treatment.

WEITZ teaches as set forth above. The reference teaches that lower molecular weight heparins (LMWHs) have utility in situations where antithrombotics are indicated, such as post-surgical prophylaxis of deep venous thrombosis. See page 371. The reference also teaches that LMWHs have greater bioavailability than standard heparins, due to decreased non-specific protein binding. See page 366, right-hand column. The reference further teaches that fibrin-bound thrombin is not inhibited by antithrombin III or HC II even in the presence of heparin, because the active site is blocked. See page 367, 1st full paragraph.

HOGG teaches that higher molecular weight heparin species (greater about 11,200) facilitate the binding of thrombin to fibrin, as set forth above.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare fractionated heparin products having MW of approximately 8000 Daltons or greater and enriched in the antithrombin pentasaccharide binding site to maximize the antithrombotic activity by both antithrombin and HC II. The artisan would be motivated to cap the upper limit the MW range of the product generally to prevent non-specific protein binding that decreases the bioavailability of higher molecular weight heparin products. The artisan would be motivated to limit the MW to about 11,200 or less to prevent the production of a ternary complex of heparin binding fibrin and thrombin, as such binding makes the active site of thrombin unavailable for inhibition. It would be further obvious to prepare a product having such a range with a low polydispersity by gel filtration in order to have a heterogeneous product with predictable properties. The recited physiological properties would naturally flow from preparation of such a product.

It would be further obvious to administer such a product for the treatment/prevention of thrombotic conditions. WEITZ had taught the suitability of LMWHs having antithrombotic activity for such treatment. Therefore, the artisan would be motivated to use the products in this manner, with the reasonable expectation that a slightly higher molecular weight fraction would have greater antithrombotic activity, due to enrichment in the pentasaccharide site and the increased length allowing HC II to thrombin binding. The artisan would reasonably expect success with such therapeutic methods.

Examiner's hours, phone & fax numbers

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (571) 272-0656. The examiner can normally be reached on Tuesday, Thursday, and Friday 7:00 to 3:30 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson (571) 272-0661, may be contacted. The fax number for Group 1600, Art Unit 1623 is (703) 872-9306.

Visit the U.S. PTO's site on the World Wide Web at http://**www.uspto.gov**. This site contains lots of valuable information including the latest PTO fees, downloadable forms, basic search capabilities and much more.

Leigh C. Maier

Leigh C. Maier
Patent Examiner
January 21, 2005